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CONTROLLED-RELEASE PHARMACEUTICAL PREPARATIONS

Abstract:

Controlled-release pharmaceutical preparations in stable particulate form prepared by spray-drying are disclosed. The controlled-release preparation may comprise one or more water-soluble pharmaceutically active compounds adsorbed to calcium or aluminium salt microparticles. Alternatively, the controlled-release preparation may comprise microspherical particles comprising a continuous matrix of biodegradable polymer containing one or more discrete regions comprising water-soluble pharmaceutically active compound(s).

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(54) Title: CONTROLLED-RELEASE PHARMACEUTICAL PREPARATIONS

(57) Abstract

Controlled-release pharmaceutical preparations in stable particulate form prepared by spray-drying are disclosed. The controlled-release preparation may comprise one or more water-soluble pharmaceutically active compounds adsorbed to calcium or aluminium salt microparticles. Alternatively, the controlled-release preparation may comprise microspherical particles comprising a continuous matrix of biodegradable polymer containing one or more discrete regions comprising water-soluble pharmaceutically active compound(s).

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CONTROLLED-RELEASE PHARMACEUTICAL PREPARATIONS

FIELD OF THE INVENTION

This invention relates to pharmaceutical preparations, and in particular it relates to pharmaceutical preparations which contain a pharmaceutically active ingredient which is released from the preparation in a controlled- or delayed-release manner. Such pharmaceutical preparations will be referred to herein as "controlled-release" pharmaceutical preparations.

BACKGROUND OF THE INVENTION

In International Patent Application No. PCT/AU93/00677 (WO94/15636), there are disclosed controlled- or delayed-release vaccine preparations which are in stable particulate form, the particles being microspherical particles which comprise a continuous matrix of biodegradable polymer (such as polylactic acid, polyglycolic acid and copolymers thereof), with one or more discrete, immunogen-containing regions (optionally also containing an adjuvant) dispersed throughout the continuous matrix. These vaccine preparations may be produced either by forming an emulsion of an aqueous suspension comprising the immunogen and optionally the adjuvant in a continuous organic phase having the biodegradable polymer dissolved therein and subsequently spray-drying the water-in-oil emulsion to form the microspherical particles, or by forming a suspension of a particulate immunogen-containing material in a continuous organic phase having the biodegradable polymer dissolved therein and then spray-drying the suspension to form the microspherical particles.

International Application No. PCT/AU93/00677 also discloses a single dose vaccine made by mixing one or more (generally two) of these controlled- or delayed-release vaccine preparations with a microparticulate, immediate-release vaccine component. In the preparation of these immediate-release vaccine components, vaccine immunogens were adsorbed to gels of aluminium salts (typically aluminium phosphate or aluminium hydroxide), optionally with a sugar stabiliser (preferably trehalose), and the mixture spray dried to form microparticles 1 to 3 μm diameter. These microparticles were shown to generate greater and longer lasting immune responses than the identical

liquid vaccine from which they were prepared, possibly due to an increased persistence of these microparticles at the injection site, thus minimising inactivation of immunogen by Kuppfer cells of the liver and maximising time of exposure to immune effector cells; i.e. the microparticulate nature of the vaccine component was generating a short-term controlled release.

In work leading to the present invention, it has been shown that pharmaceutically active drugs and other compounds can be prepared in stable particulate form to provide controlled-release pharmaceutical preparations. In addition, it has been shown that the release characteristics of these preparations can be controlled as desired by appropriate selection of the various components of the preparations.

The controlled-release pharmaceutical preparations of the present invention have particular utility in that they enable water-soluble pharmaceutically active compounds to be formulated in a manner which does not result in modification of the active compounds, which results for example from exposure to organic solvents used in the solubilisation of polymeric materials. This is of special importance where the pharmaceutically active compounds are for example proteins which might lose activity on modification of their structure.

SUMMARY OF THE INVENTION

According to one aspect of the present invention, there is provided a controlled-release pharmaceutical preparation comprising at least one water-soluble pharmaceutically active compound in stable, dry particulate form, said particles being microparticles prepared by spray-drying and comprising a calcium or aluminium salt having said pharmaceutically active compound(s) adsorbed thereon.

Preferably, the particles are microparticles of a calcium or aluminium salt gel, more preferably a calcium phosphate or aluminium phosphate gel.

This invention also provides a method for the production of a controlled-release pharmaceutical preparation as described above, which comprises the steps of contacting

the water-soluble pharmaceutically active compound(s) with a calcium or aluminium salt gel, and subsequently spray-drying the preparation to form microparticles of said calcium or aluminium salt having said pharmaceutically active compound(s) adsorbed thereon.

In this aspect of the invention, the microparticles may, for example, have a size in the range of from 1-3 μm up to 20-30 μm in diameter.

According to another aspect of the present invention, there is provided a controlled-release pharmaceutical preparation comprising at least one water-soluble pharmaceutically active compound in stable, dry particulate form, said particles being microspherical particles prepared by spray-drying and comprising a continuous matrix of biodegradable polymer containing one or more discrete regions comprising said water-soluble pharmaceutically active compound(s).

In another aspect, the invention provides a controlled-release pharmaceutical preparation comprising at least one water-soluble pharmaceutically active compound and at least one lipid-soluble pharmaceutically active compound in stable, dry particulate form, said particles being microspherical particles prepared by spray-drying and comprising a continuous matrix of biodegradable polymer with said lipid-soluble pharmaceutically active compound(s) therein, said matrix containing one or more discrete regions comprising said water-soluble pharmaceutically active compound(s).

In yet another aspect, the invention also provides a method for the production of a controlled-release pharmaceutical preparation in stable, dry particulate form as described above, which comprises the steps of forming an emulsion of an aqueous phase comprising the water-soluble pharmaceutically active compound(s) in a continuous organic phase having said biodegradable polymer dissolved therein, and subsequently spray-drying the water-in-oil emulsion to form microspherical particles which comprise a continuous matrix of polymer containing one or more discrete regions comprising the water-soluble pharmaceutically active compound(s).

Where the controlled-release pharmaceutical preparation also comprises lipid-

soluble pharmaceutically active compound(s), these compounds are dissolved with the biodegradable polymer in the continuous organic phase prior to spray-drying the emulsion.

In this aspect of the invention, the microspherical particles may have a size in the range of from 10-30 μm in diameter, preferably in the range of 20-30 μm.

It will be appreciated that the present invention also extends to a pharmaceutical composition comprising a controlled-release pharmaceutical preparation as described above, together with a pharmaceutically or veterinarily acceptable carrier or diluent. This invention also extends to a method of treating a human or other animal patient, which comprises administering to the patient a therapeutically effective amount of a pharmaceutical composition as described above.

As used herein, the terms "pharmaceutical preparation" and "pharmaceutical composition" are to be understood as including both preparations and compositions for use in treatment of humans and preparations and compositions for use in treatment of other animals.

Throughout this specification, unless the context requires otherwise, the word "comprise", or variations such as "comprises" or "comprising", will be understood to imply the inclusion of a stated integer or group of integers but not the exclusion of any other integer or group of integers.

DETAILED DESCRIPTION OF THE INVENTION

The water-soluble pharmaceutically active compound(s) in the controlled-release pharmaceutical preparations of the invention may, if desired, be stabilised with a stabiliser, in particular a sugar or sugar derivative such as trehalose, lactose, dextrose, mannitol or glucosamine.

Where the water-soluble pharmaceutically active compound(s) are present in discrete regions in a continuous matrix of biodegradable polymer, they may be adsorbed

on a solid carrier such as a calcium or aluminium phosphate gel.

The water-soluble pharmaceutically active compounds which may be formulated in accordance with this invention include all water-soluble pharmaceutical or veterinary drugs, as well as water-soluble proteins which are therapeutically active in humans and other animals such as erythropoietin, GM-CSF and other CSFs, any member of the extensive family of cytokines, e.g. IL-1, IL-2, IFN-γ, and the like, blood factors and the like, and growth factors such as bovine somatotrophin, (BST), porcine somatotrophin (PST), and the like. Other compounds include hormones such as testosterone, oestradiol and the like, and antibiotics and antimalarial drugs. The water-soluble vitamins may also be formulated in accordance with this invention (and water-insoluble or lipid-soluble vitamins may be included in the polymeric continuous matrix).

The biodegradable polymer used in the present invention may be any polymer substance which is capable of existing in a nonaqueous phase, which is biocompatible and which is capable of delayed breakdown *in vivo*. Suitable polymers include, for example polyesters, polyorthoesters, polyanhydrides and cyanoacrylates, as well as various natural polymers including some proteins and polysaccharides. Particularly suitable polymers for use in accordance with the present invention include homopolymers of D-, L- and DL-polylactic acids (D-PLA; L-PLA; DL-PLA) and polyglycolic acid (PGA), and various polylactide coglycolide (PLG) copolymers thereof.

Preferably, in the formation of the water-in-oil emulsion, one or more emulsifiers are used, and suitable emulsifiers include, for example, Tween 80 and Span 85 and mixtures thereof.

In the production of the microparticulate, controlled-release preparation of this invention, the water-soluble pharmaceutically active compound(s) is/are adsorbed to a calcium or aluminium salt gel, a sugar stabiliser is added if desired, and the preparation is spray-dried.

In the production of the microspherical, controlled-release preparation of this

invention, an aqueous phase is prepared including the water-soluble compound(s) and emulsifier(s), and this aqueous phase is then emulsified into a continuous organic phase which consists of the biodegradable polymer (and, if desired, the lipid-soluble compound(s)) dissolved in an organic solvent such as chloroform or dichloromethane. By way of example, the emulsion may comprise 1 part aqueous phase : 9 parts organic phase, by volume. The resultant water-in-oil emulsion is then spray-dried under suitable conditions, to generate the microspherical particles of the preparation of the invention. The water-soluble active compound(s) in this emulsion may be free in solution or adsorbed to a calcium or aluminium salt gel prior to emulsification.

The controlled-release preparations of this invention may be administered to a human or animal patient by any appropriate route, for example, parenterally by injection in an acceptable pharmaceutical or veterinary carrier or diluent. Alternatively, the preparation may be administered in the form of a solid pellet or implant using a solid carrier for subcutaneous or similar use.

The formulation of pharmaceutical compositions is well known to persons skilled in this field. Suitable pharmaceutically acceptable carriers and/or diluents include any and all conventional solvents, dispersion media, fillers, solid carriers, aqueous solutions, coatings, antibacterial and antifungal agents, isotonic and absorption delaying agents, and the like. The use of such media and agents for pharmaceutically active substances is well known in the art, and it is described, by way of example, in *Remington's Pharmaceutical Sciences*, 18th Edition, Mack Publishing Company, Pennsylvania, USA. Except insofar as any conventional media or agent is incompatible with the active ingredient, use thereof in the pharmaceutical compositions of the present invention is contemplated. Supplementary active ingredients can also be incorporated into the compositions.

It is especially advantageous to formulate pharmaceutical compositions in dosage unit form for ease of administration and uniformity of dosage. Dosage unit form as used herein refers to physically discrete units suited as unitary dosages for the human or other animal patients to be treated; each unit containing a predetermined

quantity of active ingredient calculated to produce the desired therapeutic effect in association with the required pharmaceutical or veterinary carrier and/or diluent. The specifications for the novel dosage unit forms of the invention are dictated by and directly dependent on (a) the unique characteristics of the active ingredient and the particular therapeutic effect to be achieved, and (b) the limitations inherent in the art of compounding such an active ingredient for the particular treatment.

A variety of administration routes are available for the controlled-release preparations of this invention. The particular mode selected will depend, of course, upon the particular condition being treated and the dosage required for therapeutic efficacy. The methods of this invention, generally speaking, may be practised using any mode of administration that is acceptable in the fields of human or other animal medicine, meaning any mode that produces therapeutic levels of the active component of the invention without causing clinically unacceptable adverse effects. Such modes of administration include oral, rectal, topical, nasal, transdermal or parenteral (e.g. subcutaneous, intramuscular and intravenous) routes. Formulations for oral administration include discrete units such as capsules, tablets, lozenges and the like.

The compositions may conveniently be presented in unit dosage form and may be prepared by any of the methods well known in the art of pharmacy. Such methods include the step of bringing the active component into association with a carrier which constitutes one or more accessory ingredients. In general, the compositions are prepared by uniformly and intimately bringing the active component into association with a liquid carrier, a finely divided solid carrier, or both, and then, if necessary, shaping the product.

Compositions suitable for parenteral administration conveniently comprise a sterile aqueous preparation containing the active component, which is preferably isotonic with the blood of the recipient. This aqueous preparation may be formulated according to known methods using those suitable dispersing or wetting agents and suspending agents. The sterile injectable preparation may also be a sterile injectable solution or suspension in a non-toxic parenterally-acceptable diluent or solvent, for example as a

solution in polyethylene glycol and lactic acid. Among the acceptable vehicles and solvents that may be employed are water, Ringer's solution and isotonic sodium chloride solution. In addition, sterile, fixed oils are conventionally employed as a solvent or suspending medium. For this purpose, any bland fixed oil may be employed including synthetic mono-or di-glycerides. In addition, fatty acids such as oleic acid find use in the preparation of injectables.

Other delivery systems can include sustained release delivery systems. Preferred sustained release delivery systems are those including a solid carrier which can provide for release of the active component in sustained release implants, pellets or capsules.

The active component is administered in therapeutically effective amounts. A therapeutically effective amount means that amount necessary at least partly to attain the desired effect, or to delay the onset of, inhibit the progression of, or halt altogether, the onset or progression of the particular condition being treated. Such amounts will depend, of course, on the particular condition being treated, the severity of the condition and individual patient parameters including age, physical condition, size, weight and concurrent treatment. These factors are well known to those of ordinary skill in the art and can be addressed with no more than routine experimentation. It is preferred generally that a maximum dose be used, that is, the highest safe dose according to sound medical judgement. It will be understood by those of ordinary skill in the art, however, that a lower dose or tolerable dose may be administered for medical reasons, psychological reasons or for virtually any other reasons.

It will be appreciated by persons skilled in the field that the present invention provides for the formulation of water-soluble pharmaceutically active compounds such as proteins, with or without additional water-insoluble (or lipid-soluble) active compounds, into a controlled-release microspherical, injectable preparation. By formulating the preparation using different biodegradable polymers, for example by using different ratios of polylactide coglycolide (PLG), and with different inherent viscosities, preparations with different release characteristics can be produced. These preparations may then be mixed in appropriate proportions to achieve an end product

having the desired final release characteristics.

In addition, the final release characteristics of the end product may be further modified by incorporation of a further component having initial short-term release characteristics and which comprises stable, dry particles comprising water-soluble pharmaceutically active compound(s) adsorbed onto microparticles of a calcium or aluminium salt.

Further features of the present invention are more fully described in the following Example(s). It is to be understood, however, that this detailed description is included solely for the purposes of exemplifying the present invention, and should not be understood in any way as a restriction on the broad description of the invention as set out above.

EXAMPLE 1

Production of a slow-release preparation of mouse-recombinant GM-CSF.

The following copolymers of polylactide coglycolide were sourced from Birmingham Polymers Ltd, Birmingham, Alabama, USA:

(i) 50:50 copolymer, inherent viscosity 0.20

(ii) 50:50 copolymer, inherent viscosity 0.30

(iii) 50:50 copolymer, inherent viscosity 0.41

(iv) 50:50 copolymer, inherent viscosity 0.47

The copolymers were solubilised to 5% w/v dissolution in either chloroform or dichloromethane. For each of these polymer solutions, an emulsion was produced which comprised:

a) 88 parts polymer solution

b) 2 parts of a 50:50 mixture of Tween 80 and Span 85

c) 10 parts of an aqueous solution of GM-CSF in trehalose (50mg/ml).

The mixture was vigorously agitated using either an ultrasonic probe or a high speed blender (e.g. a Siverson blender) to produce a stable water-in-oil emulsion with a milk-like consistency and appearance. The mean diameter of the discrete (aqueous) phase of this emulsion was around 0.5 to 1.0 μm. This emulsion was spray-dried using a Drytec Compact Laboratory Spray Dryer equipped with a 40/100/120 concentric-type nozzle at an atomising pressure of 30 psi and an outlet temperature of 35°C. The resultant microspheres had a size range around 20 to 30μm and were collected as a free-flowing powder. Traces of remaining organic solvent were removed *in vacuo* and the product was stored in a dry environment at 4°C.

EXAMPLE 2

Production of a moderate-release preparation of mouse-recombinant GM-CSF.

GM-CSF was separately absorbed to gels of aluminium phosphate and calcium phosphate by slow addition of the cytokine to the appropriate gel at the optimal pH and ionic strength whilst continuously stirring overnight. The gel was spray-dried in a Drytec Compact Laboratory Spray Dryer equipped with a 40/100/120 concentric-type nozzle. Two different preparations were made for each gel. The first used an atomising pressure of 80 psi and an outlet temperature of 60°C to achieve particles in the range 1 to 3 μm. The second used an atomising pressure of 30 psi and an outlet temperature of 60°C to achieve particles in the range of 20 to 30μm. All microparticles were stored at 4°C in a dry environment.

EXAMPLE 3

Estimation of *in vitro* release characteristics.

Preparations as described in Examples 1 and 2 were placed in buffered saline containing 2 mg/ml casein and 0.1%(w/v) sodium azide and held at 37°C . At intervals of days to weeks, depending upon the expected release characteristics of the preparation, samples of the supernatant were removed for estimation of GM-CSF content by enzyme immunoassay (EIA). Fresh diluent was added to replace the aliquot removed.

Based on the results of these experiments, calculated weights of the appropriate preparations are mixed to give a formulation with zero order release characteristics over a desired time interval.

Those skilled in the art will appreciate that the invention described herein is susceptible to variations and modifications other than those specifically described. It is to be understood that the invention includes all such variations and modifications which fall within its spirit and scope. The invention also includes all the steps, features, compositions and compounds referred to or indicated in this specification, individually or collectively, and any and all combinations of any two or more of said steps or features.

CLAIMS

1. A controlled-release pharmaceutical preparation comprising at least one water-soluble pharmaceutically active compound in stable, dry, particulate form, said particles being microparticles prepared by spray-drying and comprising a calcium or aluminium salt having said pharmaceutically active compound(s) adsorbed thereon.

2. A pharmaceutical preparation of claim 1, wherein said particles are microparticles of a calcium or aluminium salt gel.

3. A pharmaceutical preparation of claim 2, wherein said particles are microparticles of a calcium or aluminium phosphate gel.

4. A pharmaceutical preparation of claim 1, further comprising a stabiliser for said pharmaceutically active compound(s).

5. A pharmaceutical preparation of claim 4, wherein said stabiliser is a sugar or sugar derivative.

6. A pharmaceutical preparation of claim 5 wherein said stabiliser is selected from the group consisting of trehalose, lactose, dextrose, mannitol and glucosamine.

7. A pharmaceutical preparation of claim 1, wherein said microparticles have a size in the range of from 1-3 μm up to 20-30 μm.

8. A pharmaceutical preparation of claim 1, wherein the water-soluble pharmaceutically active compound is GM-CSF.

9. A method for the production of a pharmaceutical preparation of claim 1, which comprises the steps of contacting the water-soluble pharmaceutically active compound(s) with a calcium or aluminium salt gel, and subsequently spray-drying the preparation to

form microparticles of said calcium or aluminium salt having said pharmaceutically active compound(s) adsorbed thereon.

10. A controlled-release pharmaceutical preparation comprising at least one water-soluble pharmaceutically active compound in stable, dry particulate form, said particles being microspherical particles prepared by spray-drying and comprising a continuous matrix of biodegradable polymer containing one or more discrete regions comprising said water-soluble pharmaceutically active compound(s).

11. A controlled-release pharmaceutical preparation comprising at least one water-soluble pharmaceutically active compound and at least one lipid-soluble pharmaceutically active compound in stable, dry particulate form, said particles being microspherical particles prepared by spray-drying and comprising a continuous matrix of biodegradable polymer with said lipid-soluble pharmaceutically active compound(s) therein, said matrix containing one or more discrete regions comprising said water-soluble pharmaceutically active compound(s).

12. A pharmaceutical preparation of claim 10 or claim 11, wherein said water-soluble pharmaceutically active compound(s) are adsorbed on a solid carrier.

13. A pharmaceutical preparation of claim 12, wherein said solid carrier is a calcium or aluminium phosphate gel.

14. A pharmaceutical preparation of claim 10 or claim 11, further comprising a stabiliser for said water-soluble pharmaceutically active compound(s).

15. A pharmaceutical preparation of claim 14, wherein said stabiliser is a sugar or sugar derivative.

16. A pharmaceutical preparation of claim 15, wherein said stabiliser is selected from the group consisting of trehalose, lactose, dextrose, mannitol and glucosamine.

17. A pharmaceutical preparation of claim 10 or claim 11, wherein said biodegradable polymer is selected from the group consisting of polylactic acid, polyglycolic acid, and copolymers thereof.

18. A pharmaceutical preparation of claim 10 or claim 11, wherein said microspherical particles have a size in the range of from 10-30 μm, preferably from 20-30 μm.

19. A pharmaceutical preparation of claim 10 or claim 11, wherein the water-soluble pharmaceutically active compound is GM-CSF.

20. A method for the production of a pharmaceutical preparation of claim 10 or claim 11, which comprises the steps of forming an emulsion of an aqueous phase comprising the water-soluble pharmaceutically active compound(s) in a continuous organic phase having said biodegradable polymer and optionally one or more lipid-soluble pharmaceutically active compounds dissolved therein, and subsequently spray-drying the water-in-oil emulsion to form microspherical particles which comprise a continuous matrix of biodegradable polymer with said lipid-soluble pharmaceutically active compound(s), where present, therein, said matrix containing one or more discrete regions comprising said water-soluble pharmaceutically active compound(s).

21. A method of claim 20, wherein said emulsion includes an emulsifier.

22. A pharmaceutical composition comprising a controlled-release pharmaceutical preparation of any of claims 1 to 8, together with a pharmaceutically or veterinarily acceptable carrier or diluent.

23. A pharmaceutical composition comprising a controlled-release pharmaceutical preparation of any of claims 10 to 19, together with a pharmaceutically or veterinarily acceptable carrier or diluent.

24. A pharmaceutical composition of claim 23, comprising a mixture of two or more

of said controlled-release preparations, each having different release characteristics.

25. A pharmaceutical composition of claim 23 or claim 24, further comprising a controlled-release pharmaceutical preparation of any of claims 1 to 8.

26. A pharmaceutical composition of any of claims 22 to 25 in a form suitable for parenteral administration.

27. A pharmaceutical composition of any of claims 22 to 26, wherein said carrier is a solid carrier and said pharmaceutical composition is in the form of a solid pellet or implant.

28. A method of treating a human or other animal patient, which comprises administering to the patient an effective amount of a pharmaceutical composition of any of claims 22 to 27.

INTERNATIONAL SEARCH REPORT

International Application No.
PCT/AU 95/00648

A. CLASSIFICATION OF SUBJECT MATTER

Int Cl[6]: A61K 9/16, 9/18, 38/19, 47/02, 47/34

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC A61K 9/-, 47/-

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
AU: IPC as above

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
DERWENT and CHEMICAL ABSTRACTS: Keywords (micropart: or microspher: or microbcad:) and [(aluminium or Al or calcium or Ca) or (biodegrad: () polymer or bioabsorb: () polymer or Polylact: or polyglycol: or lactic or glycolic)]

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 94/15636 A1 (CSL LIMITED) 21 July 1994	1-7, 9-10, 12-18, 20-28
Y	US 5219577 A1 (NIR KOSSOVSKY et al) 15 June 1993	1-2, 7
X	EP 486959 A1 (VECTORPHARMA INTERNATIONAL SPA) 27 May 1992	10, 17, 18, 20, 21, 23, 26, 28

[X] Further documents are listed in the continuation of Box C

[X] See patent family annex

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

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"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
13 December 1995	29 December 1995
Name and mailing address of the ISA/AU AUSTRALIAN INDUSTRIAL PROPERTY ORGANISATION PO BOX 200 WODEN ACT 2606 AUSTRALIA Facsimile No.: (06) 285 3929	Authorized officer G.A. Jenkins **Gillian Jenkins** Telephone No.: (06) 283 2252

Form PCT/ISA/210 (second sheet) (July 1992) copkjy

INTERNATIONAL SEARCH REPORT

International Application No.
PCT/AU 95/00648

C (Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	WO 90/01949 A1 (THE AUSTRALIAN NATIONAL UNIVERSITY) 8 March 1990	1-3, 7, 22, 26, 28
X	Journal of Controlled Release, Volume 32, 1994, pages 79-85, Shigeyuki Takada et al. "Preparation and characterization of copoly (dl-lactic/glycolic acid) microparticles for sustained release of thyrotropin releasing hormone by double nozzle spray drying method".	10, 14-18, 20, 23, 26, 28
Y	International Journal of Pharmaceutics, volume 95, 1993, pages 77-83, Lucy S.C. Wan et al. "Influence of hydrophile-lipophile balance on alginate microspheres".	1-2, 7, 9
X	Journal of Controlled Release, Volume 26, 1993, pages 229-238, P.K. Gupta et al. "In vitro and in vivo evaluation of clarithromycin/poly(lactic acid)microspheres for intramuscular drug delivery".	10, 17, 18, 20, 23, 26, 28
X	Journal of Pharmacy and Pharmacology, Volume 40, 1988, pages 754-757, Roland Bodmeier et al. "Preparation of biodegradable poly (±) lactide microparticles using a spray-drying technique".	10, 17, 18, 20, 23

INTERNATIONAL SEARCH REPORT

...ernational Application No.
PCT/AU 95/00648

Box 1 Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a)

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. Claims 1-9, 22, 26-28
Microparticles comprising pharmaceutically active compound adsorbed onto a calcium or aluminium salt.

2. Claims 10-21, 23-28
Microparticles comprising pharmaceutically active compound in continuous matrix of biodegradable polymer.
See reasoning on extra sheet.

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims

2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.

☒ No protest accompanied the payment of additional search fees.

Box II continued

The international application does not comply with the requirements of unity of invention because it does not relate to one invention or to a group of inventions so linked as to form a single general inventive concept. In coming to this conclusion the International Searching Authority has found that there are two inventions:

A. Claims 1-9, 22, 26-28 define a controlled-release pharmaceutical preparation of at least one water-soluble pharmaceutically active compound in the form a stable, dry microparticles prepared by spray-drying. The microparticles comprise the active compound adsorbed onto a calcium or aluminium salt such as the phosphate gel. A preferred size range for the microparticles is from 1-30μm.

B. Claims 10-21, 23-28 also define a controlled-release pharmaceutical preparation of at least one water-soluble pharmaceutically active compound in the form of stable, dry, microspherical particles prepared by spray-drying. However, in these claims the microparticles comprise a continuous matrix of biodegradable polymer (for example polylactic or polyglycolic acids) containing one or more discrete regions comprising the active compound. A preferred size range for the microparticles is from 10-30μm. These microparticles may, in addition include a lipid-soluble pharmaceutically active compound which forms part of the polymer matrix.

Microparticles (with particle sizes as small as about 2μm) comprising pharmaceutically active compounds formed by spray drying are well known in the pharmaceutical industry -see, for example, Perry's Chemical Engineers' Handbook, sixth edition, editors Robert H Perry and Don W Green, published by McGraw-Hill Book Company, 20-54 to 20-58 and Spray Drying Handbook, fifth edition, Keith Masters, published by Longman Scientific and Technical.

It is considered that the special technical feature defined in claims 1-9 is that the microparticles comprise the active compound adsorbed onto a calcium or aluminium salt. The special technical feature defined in claims 10-28 is considered to be that the miroparticles comprise a continuous matrix of biodegradable polymer containing one or more discrete regions comprising the active compound. The special technical features are not common to each set of claims, nor can they be considered to be equivalent. Release of active agent adsorbed onto a calcium or aluminium salt will be quite different to release from the discrete regions in a biodegradable polymer matrix.

Since the above mentioned groups of claims do not share either of these special technical features, a "technical relationship" between the inventions, as defined in PCT rule 13.2 does not exist. Accordingly the international application does not relate to one invention or to a single inventive concept.

INTERNATIONAL SEARCH REPORT
Information on patent family members

International Application No.
PCT/AU 95/00648

This Annex lists the known "A" publication level patent family members relating to the patent documents cited in the above-mentioned international search report. The Australian Patent Office is in no way liable for these particulars which are merely given for the purpose of information.

Patent Document Cited in Search Report		Patent Family Member					
WO	94/15636	AU	58053/94	CA	2152949	EP	678035
US	5219577	AT	104546	AU	79210/91	CA	2045204
		DE	69101753	EP	465081	ES	2055539
		JP	5255111	PT	98066	US	5334394
		US	5462750	US	5178882	US	5306508
		US	5441739	US	5460830	US	5460831
		US	5462751	US	5464634	AU	56009/94
		AU	57266/94	AU	69544/94	CA	2152490
		EP	676954	EP	676955	WO	9415581
		WO	9415585	WO	9415586	WO	9512392
		WO	9528915				
EP	486959	EP	486763	IT	9022155	IT	1243390
		JP	4283510				
WO	90/01949	AU	41876/89	CA	1337047	DE	68922109
		EP	431023	JP	4501105		

END OF ANNEX